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~~ZISKA, S~~	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/7/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), four (4) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-42 are pending in the application.
   Of the above, claims 8-22 & 32-42 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-7, 23-31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

This application should be reviewed for errors.

Claims 1-7 and 23-31 are active and examined in this Office Action.

Applicant's election without traverse of Group I, claims 1-7 and 23-31 in Paper No. 7 is acknowledged.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and or use the invention as claimed, i.e., failing to provide an enabling disclosure. Case law teaches (Ex parte Forman, 230 USPQ 546, 547 (PTO Bd. App. Int. 1986)that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims". The specification discloses that EGF infusion into the subependymal lateral ventricle in vivo resulted in the proliferation and migration of precursor cells located in the subependyma in response to the growth factor. The specification fails to disclose administration of Bcl-2 to the same site. There is no evidence in the specification that Bcl-2 administered as a protein would be taken up by the intended target cells. The

specification discloses use of the Bcl-2 gene, not the protein, and the uptake mechanisms of DNA and proteins are known in the art to be different. One of skill in the art would not expect that the Bcl-2 protein would be internalized since there is no evidence presented that the intended target cells have receptors for Bcl-2 or would ingest Bcl-2 via nonspecific mechanisms (phagocytosis, for example) in their quiescent state. The specification fails to provide evidence that the bcl-2 protein would be taken up and exert the claimed effects. Therefore, the specification is not enabling for the method of claim 7.

Regarding claims 1-7 and 23-31, the specification is not enabling for the practice of the invention in humans and the claims must be limited to non-human mammals. The specification fails to provide guidance regarding the treatment of humans since there is no disclosure regarding the sites of implantation of the mini-pumps, the amount to administer, the time course of administration, evidence of similarity between human and mouse cell types in the subependymal cells and length of treatment necessary to effect a response. Regarding claims 23-31, the specification fails to disclose treatment of neural degeneration in humans and the claims must be limited to non-human mammals. The specification merely alludes to the potentially therapeutic usefulness of such an approach and fails to provide evidence that the invention would work as claimed in humans since the specification fails to provide the guidance enabling one of skill to apply the invention to humans. For example, the specification fails to provide guidance for determining the actual pump size for implantation which is done by determining the amount of biological activity required for the particular application. In the case of pumps releasing therapeutic substances, standard dosage considerations and criteria must be considered. Factors to be considered include the size and weight of the recipients, the

productivity or functional level of the pumps and the normal productivity or metabolic activity of the organ or tissue whose function is being replaced or augmented, in this case, the precursor cells. In view of the unpredictability as seen in treatments of neural diseases of other experimental animals such as rats and monkeys, and in view of the lack of experimental results in humans, the specification is not enabling for the practice of the invention in humans. The phrase "neurological disorder" is broad and covers a wide variety of human neurological ailments such as Huntington's Disease and Alzheimers' Disease. Applicants have failed to provide evidence that administration of EGF, for example, would treat any and all neurological disorders of humans and it would require undue experimentation by one of skill to determine the amount of EGF required to treat neurological disorders in humans since there is no teaching either in the specification or the art that EGF deficiency is causative of neural degeneration or that addition of EGF will treat all the neurological disorders. Emerich (Cell Transplantation) discloses that the treatment of neurodegenerative disorders is unpredictable and that neural transplants do not necessarily produce behavioral recovery and in some cases have either no beneficial effects, magnify existing behavioral abnormalities or even produce a unique constellation of deficits. Although Emerich is discussing transplantation of fetal neural tissue, the same arguments may be made when using genetically engineered cells to produce the neural factors, or protein-treated cells (claims 29-31) which are then reimplanted. Emerich further discloses neurodegenerative diseases produce unique patterns of behavioral symptoms which are associated with the destruction of specific neuronal populations and that while we are gaining an understanding of the pathology and molecular biology of these disorders, there remains a wide gap between our

understanding of the neural substrates of these disorders and our ability to effectively prevent or treat them. Emerich discloses that for example, regarding Parkinson's Disease, the current pharmacological strategy on increasing the striatal dopamine levels by administration of L-dopa has met with limited long term success and may even result in deleterious side effects. Emerich discloses that the extent of functional recovery in the animal models depended on the location of the transplanted tissue and the subsequent compartmentalization of dopamine release. By analogy, then, the method of treatment of a neurological disorder as claimed in claims 23-31 would also depend upon the disease and the location of the mini-pump. Note that claim 23 does not contain the limitation of a minipump and therefore the method of claim 29 does not include the continuous release from a pump. There is no evidence in the specification that treatment of the cells per se before implantation would be effective for any type of therapy since there is no evidence that a single exposure of the cells to any number of growth factors would enable the cells to differentiate or develop along the desired pathway. The specification is not enabling for the scope of the claims for treatment of "neurological disorders" in view of the lack of guidance regarding the neural substrates for the disorders, lack of evidence that the amount of EGF produced and taken up by the cells would be therapeutically effective for the disease and lack of evidence that any biochemically manipulated cell would be capable of any particular level of expression. It would require undue experimentation by one of skill to practice the invention as claimed in view of the lack of guidance and breadth of the claims.

Claims 1-7 and 23-31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1, 2 and 4-6 are rejected under 35 U.S.C. § 103 as being unpatentable over Morshead et al. (Journal of Neuroscience, 1992) and Smart taken with Williams et al. and Morrison et al. Morshead discloses a method for the in situ proliferation of CNS precursor cells. Morshead discloses examining the proliferation kinetics and fates of the mitotically active cells in the subependymal layer of mice and discloses that the results suggest that one of the progeny from each cell division dies and that 33% of the subependymal cells continue to proliferate in adult life. Smart discloses (page 326)that the subependymal layer is a

collection of undifferentiated, mitotically active cells which appears during embyronic development, plays an important part in the production of cells for the cerebral cortex and persists into adult life retaining, at least in rats and mice, its ability to form new cells. Smart discloses (page 325) that the subependymal layer is considered to remain a potential source of undifferentiated cells which can give rise to neoplasms and that a layer similar to the human subependymal layer has been described in rats and mice and that an outstanding feature of the layer in these animals is the persistence of a high rate of mitotic activity apparently indefinitely into adult life. Smart further discloses (page 337, column 1) that the development of the subependymal layer provides a large reservoir of undifferentiated neuroblasts which are able to divide and migrate actively and thus produce the millions of neurons which form the cortical areas of the brain and (column 2) that by adult life the once burgeoning layer is reduced to a degenerate remnant which nevertheless continues to form new cells indefinitely after the need has passed. Smart therefore discloses that the subependymal cells are CNS precursor cells. Morshead concluded that the proliferating cells of the subependyma divide in a stem cell mode with one postmitotic cell from each division dying. Morshead and Smart differ from the claims in that the reference fails to disclose administration of EGF to stimulate in situ proliferation. However, the secondary references, Williams et al. and Morrison et al., cure the deficiency. Morrison discloses the EGF enhances survival of neonatal rat brain cells in a dose dependent manner and that the effect was dependent upon the continuous presence of EGF in the medium. Morrison discloses the EGF binding sites occur in brain tissues, thus indicating that EGF is a naturally binding growth factor to CNS cells. Williams discloses use of a minipump to administer the growth factor.

Williams discloses continuous infusion of nerve growth factor into rats and that continuous treatment with nerve growth factor prevents neuronal death.

It would have been obvious to one of ordinary skill to modify the method of Morshead by the administration of EGF to stimulate the proliferation of the CNS precursor cells in view of the teachings of Morrison that EGF stimulates the proliferation and differentiation of CNS cells and the teachings of Morshead and Smart that the ependymal cells serve as a reserve source of undifferentiated cells in case of damage to brain tissue. It would have been obvious to one of ordinary skill to modify the method of Morshead, Smart and Morrison by using a mini osmotic pump to administer the growth factor in view of the teachings of Williams that other neural growth factors had been successfully administered using such pumps. One of ordinary skill would have been motivated to use the pumps in view of their known capability for maintaining continuous, regulatable infusion and in view of the teachings of Morrison that the EGF-effect seen was dependent upon its continuous presence. Therefore, both the motivation and the reasonable expectation of success are found in the prior art references and the references as a whole render obvious the addition of growth factors by using implanted osmotic pumps.

Regarding claims 5 and 6, Morshead discloses injection into the lateral ventricle for labelling studies. It would have been obvious to one of ordinary skill to also administer the growth factor to the central canal if the location has the subependymal region, lacking evidence to the contrary, since the subependymal region contains the progenitor cells.

Accordingly, the modification of the method of Morshead and Smart by administering EGF as suggested by Morrison via a minipump as suggested by Williams in order to obtain a method for the in situ proliferation of CNS precursor cells was within the

ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 3 is rejected under 35 U.S.C. § 103 as being unpatentable over Morshead, Smart taken with Williams and Morrison as applied to claims 1, 2 and 4-6 above, and further in view of Cattaneo et al. Claims 1, 2 and 4-6 were rejected for reasons as stated above. Cattaneo discloses that exposure of neuronal precursor cells to fibroblast growth factor promoted the proliferation and/or survival of nestin+ positive cells during in vitro culture. Cattaneo discloses that cells which are nestin+ are stem cells. It would have been obvious to one of ordinary skill to modify the method of Morshead, Smart, Morrison and Williams by administering bFGF in view of the teachings of Cattaneo that bFGF promoted the proliferation and survival of stem cells. One of ordinary skill would have been motivated to modify the method of Morshead and Smart by administering bFGF in view of the teachings of Morshead and Smart that the ependymal cells serve as a reserve source of undifferentiated cells in case of damage to brain tissue and in view of the teachings of Cattaneo that bFGF promotes proliferation of stem cells. One of ordinary skill would be motivated to proliferate the stem cells since stem cells are known to give rise to all neural cell types and therefore proliferation of stem cells would facilitate healing of damaged brain tissue.

Claim 7 is rejected under 35 U.S.C. § 103 as being unpatentable over Morshead, Smart taken with Morrison and Williams as applied to claims 1, 2 and 4- 6 above, and further in

view of Williams et al (Cell). Claims 1, 2 and 4-6 were rejected for reasons as stated above. Williams (Cell)discloses that the Bcl-2 gene is involved in apoptosis, also known as programmed cell death, and the expression of the gene product (protein) prevents cell death, resulting in immortalization. It would have been obvious to one of ordinary skill to administer the Bcl-2 protein to cells of subependymal layer since Morshead discloses that the dividing stem cell produces two daughter cells and that one of the daughter cells dies. Administration of the Bcl-2 protein would prevent the postmitotic cell death of the constitutively proliferating cells, lacking evidence to the contrary. One of ordinary skill would have been motivated to administer the bcl-2 protein to induce the proliferation of CNS precursor cells for amelioration of brain damage in view of the teachings of Morshead that the subependymal cells may serve as a source of undifferentiated cells in case of damage to brain tissue. One of ordinary skill would be motivated to proliferate the stem cells since stem cells are known to give rise to all neural cell types and therefore proliferation of stem cells would facilitate healing of damaged brain tissue.

Claims 23-28 are rejected under 35 U.S.C. § 103 as being unpatentable over Morshead and Smart taken with Morrison, Williams and Cattaneo as applied to claims 1-7 above and further in view of Gage. Claims 1-7 were rejected for reasons as stated above. Gage discloses a method for treating a neurological disorder. Gage discloses that unaltered cells are routinely transplanted as an additional approach to CNS therapy (columns 1-2). It would have been obvious to one of ordinary skill to modify the method of Morshead, Smart, Morrison, Williams and Cattaneo by transplanting autologous cells to treat a neurological disorder such as Parkinson's disease in view of the teachings of Gage that localized addition of growth factors or therapeutic agents,

delivered by transplanted cells, will treat the disease (column 2, lines 49-64).

Regarding claims 29-31, Gage discloses that a recently developed model of gene therapy uses target cells removed from a subject, placed in culture, genetically modified in vitro and then reimplanted into the subject (column 4, lines 53-68). However, Gage also discloses implanting of non-genetically modified cells which exert beneficial effects in column 16, second paragraph, and discloses grafting of autologous tissue in column 13. It would have been obvious to one of ordinary skill to modify the method of Morshead, Morrison, Williams and Smart, by implanting autologous precursor cells in view of the teachings of Smart, who discloses (page 326) that the subependymal layer is a collection of undifferentiated, mitotically active cells which appears during embyronic development, plays an important part in the production of cells for the cerebral cortex and persists into adult life retaining, at least in rats and mice, its ability to form new cells. Smart further discloses (page 337, column 1) that the development of the subependymal layer provides a large reservoir of undifferentiated neuroblasts which are able to divide and migrate actively and thus produce the millions of neurons which form the cortical areas of the brain. One of ordinary skill would have been motivated to administer growth factors to autologous cells to induce the proliferation of CNS precursor cells for amelioration of brain damage in view of the teachings of Morshead that the subependymal cells may serve as a source of undifferentiated cells in case of damage to brain tissue. One of ordinary skill would be motivated to proliferate the stem cells since stem cells are known to give rise to all neural cell types and therefore proliferation of stem cells would facilitate healing of damaged brain tissue.

Accordingly, the modification of the method of Morshead, Smart, Williams, Cattaneo and Morrison to treat a neurological disorder by culturing autologous cells ex vivo and then reimplanting the cells as suggested by Gage was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
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